Int J Cancer Manag. 2018 October; 11(10):e68915. doi: 10.5812/ijcm.68915.

Published online 2018 October 7. **Review Article**

Pros and Cons of Intraoperative Radiotherapy: Comparison of Two Clinical Trials in Breast Cancer Management

Mohammad Esmaeil- Akbari [1], Nahid Nafissi [2,*], Seyed Rabie Mahdavi [3], Hamidreza Mirzaei [4], Fattaneh Ziyayi [1], Hamid Reza Baghani [5] and Mohammmad Hosein Kalantar Motamedi [6]

[1]Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Breast Surgery, Iran University of Medical Sciences, Tehran, Iran
[3]Medical Physics Department, Iran University of Medical Sciences, Tehran, Iran
[4]Radiation Oncology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Physics Department, Hakim Sabzevari University, Sabzevar, Iran
[6]Trauma Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

[*]*Corresponding author*: Nahid Nafissi, Department of Breast Surgery, Iran University of Medical Sciences, Tehran, Iran. Tel: +98-9121939395, Email: nahid.nafissi@gmail.com

Received 2018 March 26; **Revised** 2018 August 27; **Accepted** 2018 September 11.

Abstract

Context: Intraoperative radiotherapy (IORT) is an accepted standard treatment for early stages of breast cancer in the selected cases. This is proven in two large clinical trials including ELIOT and TARGIT-A ones, which are based on high energy electron beam and low kV X-ray energy, respectively. Published results of two trials aimed at evaluating the local recurrence as the final outcome. In ELIOT study, the local recurrence rate is 4.4% versus 0.4% in patients, who received IORT and External Beam Radiotherapy (EBRT), in comparison to 3.2% and 1.3% in TARGIT-A trial. These differences need to be further evaluated regarding the efficacy and beneficence of IORT.

Objectives: The aim of this study is to further analyze the data of these two trials to confirm the strategy of IORT in breast cancer as boost or radical modality.

Evidence Acquisition: Two main breast IORT trials were considered in this study. To this end, a computerized search was performed through MEDLINE, PubMed, PubMed Central, ISI web of knowledge, and reference list of related articles. All of the published data from these trials were gathered and their subjects were analyzed and compared.

Results: Statistical analysis revealed that in patients with matching clinical, pathological, and biological profiles in both trials, radical IORT using either electron or low kV X-ray is effective and acceptable. It seems that in patients with low risk factors, IORT is more effective than EBRT. Patient selection according to America Society of Radiation Oncology or European Society of Radiation Therapy classification guidelines confirmed that the local recurrence rate of ELIOT in low risk patients, similar to TARGIT, was less than 1.9%.

Conclusions: We compared the ELIOT and TARGIT-A trial documents and found all of similarities and differences referred to these two trials recommend, using IORT for selected cases of breast cancer with at least non inferiority in Disease free survival (DFS) and overall survival (OS) as well as superiority in cosmetic, non-breast cancer death, and more.

Keywords: Breast Cancer, Intraoperative Radiotherapy, ELIOT, TARGIT-A, Local Recurrence

1. Context

Adjuvant radiotherapy is mandatory after breast conserving surgery. The addition boost dose to tumor bed in conjunction with the whole breast irradiation will decrease the risk of local recurrence. This process requires more than 30 days of daily attendance to radiotherapy, 4 to 6 months after surgery.

Intraoperative radiotherapy (IORT) for partial breast irradiation is a new innovative tool to deliver optimal dose of radiotherapy immediately after excision of cancer to well-vascularized tissue and to the margins of resection at the same operation to destroy all cancer cells that may remain around the tumor without any delay as radical irradiation for specific cases or as boost dose for others.

The first experience in IORT was established by Comas and Prio in 1905 for a case of endometrial cancer (1).

Other modalities using low energy X-ray were set upped in abdominal, thoracic, and head and neck malignancies between the 1930s and 1950s (2, 3). The modern approach to IORT started in 1960s at the University of Kyoto with studies of Abe, who used a high single fraction of radi-

ation dose from a cobalt unit and electrons from a Betatron for gastric cancer. In this technique, large single doses of radiation are administered to the patient during surgery, and most patients received no follow-up external radiation treatment (4).

About 30 years ago, Calvo (HGUGM Programme) prepared an operating room (OR) in radiation oncology department of Madrid University, where surgical procedures were performed on IORT candidates. The distance from the OR to the accelerator room was 50 meters (5).

Then, in 1970 in-room, conventional linear accelerators were used in dedicated operating rooms at the Howard University Hospital and the Massachusetts General Hospital. They prepared one of their conventional therapy rooms for intraoperative electron radiotherapy (IOERT); after surgery in the OR they transported the patient to the radiation device that was fixed on the wall (6, 7). The employed electron beam, improved IORT dose distributions, limited penetration beyond the tumor, delivered the required dose much more rapidly, and the normal tissues were effectively spared due to the limited range of electron beyond the tumor, but the risk and complexity of transferring the anesthesia patient was problematic.

In the early 1990, mobile dedicated electron accelerators and miniaturized low-energy X-ray machines were introduced into clinical practice worldwide to solve these problem.

Two comprehensive clinical trials including TARGIT-A and ELIOT trial were developed in Europe after 2000s, which employed these machine for partial breast irradiation (PBI) after breast conserving surgery.

This article is a comparative study, which focuses on the differences between these two big clinical trials in breast cancer management and further evaluating their outcome to introduce the real efficiency of IORT with X-ray and electron beam in the similar cases.

2. Evidence Acquisition

This article compares two trials in intraoperative breast radiation therapy, one using X-ray beam and the other using electron beam. We focused on these two as well as other studies that were explicitly related to these clinical trials. To extract the interested studies, we performed an iterative search in MEDLINE, PubMed, PubMed Central, and ISI Web of Knowledge databases from December 2015 to January 2018. The reference list of each article was reviewed to expand literature selection. Then, based on standard search strategies including title screening, abstract review, and scanning the method and conclusion parts of each paper, interested studies were selected. Finally, all the data related to these two clinical trials were gathered and, then, their subjects were arranged and compared without new analysis on their outcomes.

3. Results

ELIOT was done at one center (European Institute of Oncology in Milan) on 1305 patients from 2000 to 2007 (8).

TARGIT-A was a multi-centric study in 11 countries (33 centers) on 3451 cases from 2000 to 2012. In this study, 1721 cases took IORT and 15.2% of this group underwent External beam radiotherapy after definitive pathologic report, which was not excluded from final analysis. 1730 cases also underwent EBRT without any IORT in the operating room (9-11).

In the ELIOT study, 651 cases were in IORT and 654 cases were in EBRT group and the patients, who needed EBRT after IORT, were excluded from final analysis.

In TARGIT-A, X-ray with 50 kV energy was employed and dose of 20 Gy was delivered to the surface, and 5 - 7 Gy to 1 cm depth, in the time interval of 20 to 45 minutes, using spherical applicator diameters of 1.5 to 5 cm. In the ELIOT study, the electron beam with 4 - 12 MeV was used and 21 Gy dose delivered through 4 to 8 cm diameter cylindrical applicators during 3 to 5 minutes. The comparison between the overall characteristics of each clinical trial is presented in Table 1.

We matched the cases in the two groups according to age, tumor size, grade, lymph node involvement and biologic markers.

In both studies, the percentage of patients younger than 50 years were only 7%, the cases older than 70 years were 10% in ELIOT and 15% in TARGIT-A groups (P = 0.001), and the remainder were between 50 and 70 years.

Tumor size is one factor for choosing boost or whole radiotherapy in the operating room. In ELIOT study, only 31% of cases had less than 1 cm tumor size, while in TARGIT-A, 39% of cases were involved in this category. The number of cases, who had more than 2 cm tumor size, were the same and equal to 12% to 13% in both studies.

Tumor grade 1 had the same percentage of 31% to 35% in both studies, but grade 3 was more in ELIOT, 20% versus 15% in TARGIT-A (P = 0.003), and this is one of the risk factors for recurrence.

The most common histologic type in both groups was invasive ductal carcinoma, but cases with invasive lobular carcinoma was twice in ELIOT study in comparison to the TARGIT-A one (8% versus 4% (P = 0.0003)).

The number of negative lymph node cases was 74% in ELIOT study, while 84% cases were involved in TARGIT-A one, which is so good prognostic factor for TARGIT-A study. Node positivity (1 - 3 positive nodes) was near twice in ELIOT study in comparison to the TARGIT-A one (21% versus 14% (P

Table 1. ELIOT and TARGIT-A Study Comparison

Subject	ELIOT	TARGIT-A
Whole number in	1305	3451
Number of centers	Single in Milan	33 centers in 11 countries
Time	2000 - 2007	2000 - 2012
Number of IORT group	651	1721
Number of EBRT group	654	1730
EBRT after IORT	Exclude	15.2%
Radiation type	Electron	X-ray
Applicator	4 - 8 cm diameter (cylindrical)	1.5 - 5 cm diameter (spherical)
Energy	4 - 12 MeV	50 kV
Time	3 - 5 minutes	20 - 45 minutes
Dose	21 Gy	20 Gy at surface

= 0.001)). Considered tumor features in both studied trials are presented in Table 2.

Totally, the favorable characteristics such as old age, small tumor size, and negative lymph nodes were significantly better in TARGIT-A in comparison to the ELIOT study. The margin status was unclear in ELIOT study, but the reports of TARGIT-A showed that the 90.5% and 90.2% of the cases were free ink margin in IORT and EBRT groups, respectively. In both groups, near 5% of margins were positive for invasive cancer and rate of re-excision was 7% to 9% totally. Favorable characteristics of involved patients in both clinical trials are reported in Table 3.

Hormone therapy was used as adjuvant treatment in most cases of both trials: 75% in ELIOT and 65% in TARGIT-A, although more than 90% of their patients were ER positive. Type of hormone therapy and involved patients for each one is presented in Table 4.

Meanwhile, only 8% to 10% of the cases take chemotherapy in both studies, regardless the fact that more than 15% of patients were LN positive.

The recurrence rate for IORT and EBRT was 4.4% and 0.4%, respectively, in ELIOT study (Hazard Ratio = 9.3), where 2.5% of the cases were true recurrence and 1.9% were new cancer out of index quadrant for IORT (in contrast to the second group [EBRT] that there was not any new cancer). Nevertheless, if the high-risk group is excluded from the IORT, the recurrence rate was only 1.5% in 452 cases, and in patients with risk factors (199 cases 30.6%), this rate was 11.3%.

The rate of recurrence in TARGIT study was 3.3% versus 1.3% in EBRT as whole group, but in pre-pathologic group, who took IORT concurrently with surgery, this rate was 2.1% versus 1.1% (P = 0.31) without any significant difference (refer to Figures 1 and 2).

As described in these trials, 15.2% (239 of 1 571) of IORT group took EBRT after pathologic report as supplement when free margin was less than 1 mm and unexpected lobular carcinoma or extensive in-situ component was involved. In some centers, they increased these characters to put patients in this group: free margin 1 to 10 mm, several positive lymph node, and extensive lymphovascular invasion.

In the discussion about the recurrence rate in ELIOT study, unfavorable characteristics were introduced as T > 2 cm, 4 or more positive lymph nodes, grade 3, negative estrogen receptors, and triple negative cases who took only IORT.

These criteria in TARGIT-A study were tumor size more than 2 cm, any positive lymph node, grade 3, and young age, most of which took EBRT after pathologic report.

In TARGIT-A study, 67% (1 140) of the cases had undergone IORT at the same time of surgery and rest of them (33%) took IORT as second stage when the cases were sent to another center for IORT in less than 30 days after first operation. This means that 33% of the patients had two surgeries and in the second operation, the wound was only opened for IORT (post pathologic). The results showed that these two groups had great difference in recurrence rate.

In the second group, the recurrence rate was 5.4% in IORT versus 1.7% in EBRT group with major difference of 1.39% (P = 0.069). This difference is due to the tumor microenvironment change in the first surgery after X-ray radiation to tumor bed.

The rate of distant metastasis did not have major difference in both studies (between 4.8%-5.1% in ELIOT trial and 3.2% - 3.9% in TARGIT-A one).

Risk of local and regional recurrence as well as the 5 distant metastasis rate for both trials understudy are reported

Table 2. Tumor Characteristics in Trials Understudy[a]

Subject	ELIOT		TARGIT-A	
	IORT	EBRT	IORT	EBRT
Age				
< 50	44 (7)	43 (7)	150 (9)	122 (7)
50 - 70	545 (84)	536 (82)	1308 (76)	1355 (79)
> 70	62 (10)	75 (11)	263 (15)	253 (15)
Tumor size, cm				
< 1	199 (31)	194 (30)	611 (39)	597 (39)
1 - 2	363 (56)	350 (54)	751 (48)	726 (48)
> 2	83 (13)	103 (16)	190 (12)	207 (14)
Unknown	-	-	169 (10)	200 (12)
Grade				
I	196 (31)	160 (25)	528 (35)	558 (37)
II	305 (48)	328 (52)	757 (50)	720 (48)
III	129 (20)	145 (23)	232 (15)	227 (15)
Unknown	-	-	194 (11)	225 (13)
Histology				
IDC	524 (81)	514 (79)	1012 (95)	1018 (94)
ILC	53 (8)	57 (9)	47 (4)	45 (4)
Mixed	17 (3)	21 (3)	32 (3)	35 (3)
Others	53 (8)	55 (9)	43 (4)	40 (4)
ER				
Positive	583 (91)	589 (92)	1441 (92)	1433 (94)
Positive LN				
None	478 (74)	471 (73)	1307 (83)	1303 (85)
1 - 3	138 (21)	138 (21)	219 (14)	211 (14)
> 3	31 (5)	38 (6)	43 (3)	29 (2)
Unknown	-	-	152 (9)	187 (11)

Abbreviations: Invasive ductal carcinoma (IDC), Invasive lobular carcinoma (ILC), Estrogen receptor (ER), Lymph node (LN)
[a] Values are expressed as No. (%).

in Table 5.

In contrast to the recurrence rate, The 5-years survival rate in the ELIOT study was shown to be equal in both IORT and EBRT, the total death in IORT and EBRT groups was 3.2% and 3.1%, respectively (P = 0.59). In the TARGIT-A study, total death in TARGIT and EBRT group was 3.9% and 5.3%, respectively.

In TARGIT-A study, the mortality rate for IORT and EBRT groups was 2.9% and 1.9% (P = 0.056), respectively. But, the results of statistical analysis showed that non-breast cancer death (like cardiovascular or other cancer deaths) was significantly less in IORT group, who did not undergo EBRT, (1.4% versus 3.5% in EBRT, P = 0.086).

In ELIOT study, non-breast cancer death in both groups was 1.1% in 11 cases, and breast cancer death was 2.1% in IORT versus 2% in EBRT group.

The rate of breast and non-breast cancer death (mortality) for both ELIOT and TARGIT-A trials are presented in Table 6.

Local recurrence rate, after breast conserving surgery (BCS) plus EBRT for some important studies are reported in Table 7 (1, 2, 8, 12, 13). As seen in this table, the rate of local recurrence is around 3% to 6%, so as the authors of ELIOT study concluded that 0.4% is much low rate for EBRT in this study and 4.4% of recurrence in IORT group is related to other risk factors and is not so much more than other stud-

Table 3. Favorable Characteristics in IORT Groups of Both Studies

Subject	ELIOT[a]	TARGIT-A[a]	P Value
Age, y			
> 70	62 (10)	263 (15)	0.001
Tumor size, cm			
< 1	199 (31)	611 (39)	0.0003
Grade			
III	129 (20)	232 (15)	0.003
Histology			
IDC	524 (81)	1012 (95)	< 0.001
ILC	53 (8)	47 (4)	0.0003
LN+			
Negative	478 (74)	1307 (83)	< 0.001
1 - 3 pos	138 (21)	219 (14)	0.001
> 3 pos	31 (5)	43 (3)	0.019

Abbreviations: Invasive ductal carcinoma (IDC), Invasive lobular carcinoma (ILC), Lymph node (LN).
[a] Values are expressed as No. (%).

Table 4. The Status Adjuvant Therapy (Hormone Therapy) in Studied Clinical Trials[a]

Subject	ELIOT		TARGIT-A	
Adjuvant therapy	**IORT**	**EBRT**	**IORT**	**EBRT**
Endocrine therapy	489 (75)	485 (74)	727 (65)	753 (67)
Chemotherapy	53 (8)	47 (7)	116 (10)	141 (13)
Both treatment	84 (13)	96 (15)	-	-
Other	-	-	48 (4)	41 (4)
Control/unknown	26 (4)	25 (4)	100 (9)	89 (8)

[a] Values are expressed as No. (%).

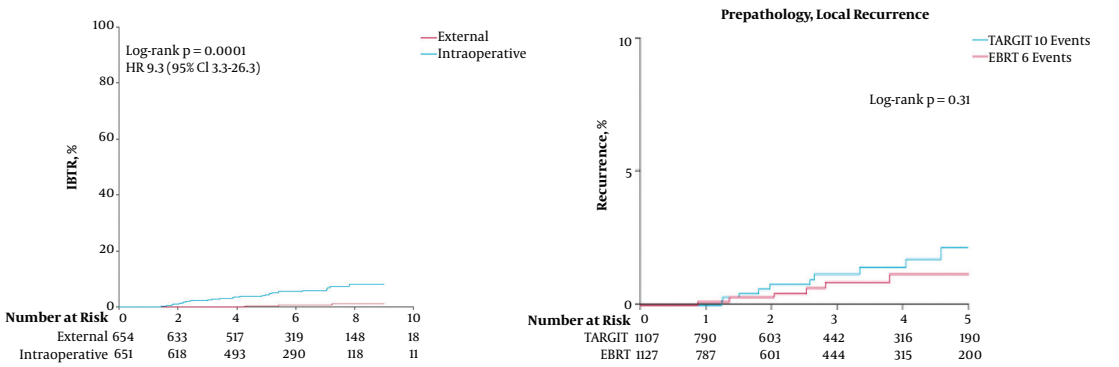

Figure 1. Local recurrence in ELIOT (Left) and pre-pathologic of TARGIT-A (Right) [with permission].

ies.

Generally, 30.6% of the cases in ELIOT study had unfavorable characteristics, but only 8% received chemotherapy and 13% received both Hormone therapy (HT) and chemotherapy. It means that approximately 10% of high-risk group did not take appropriate adjuvant therapy.

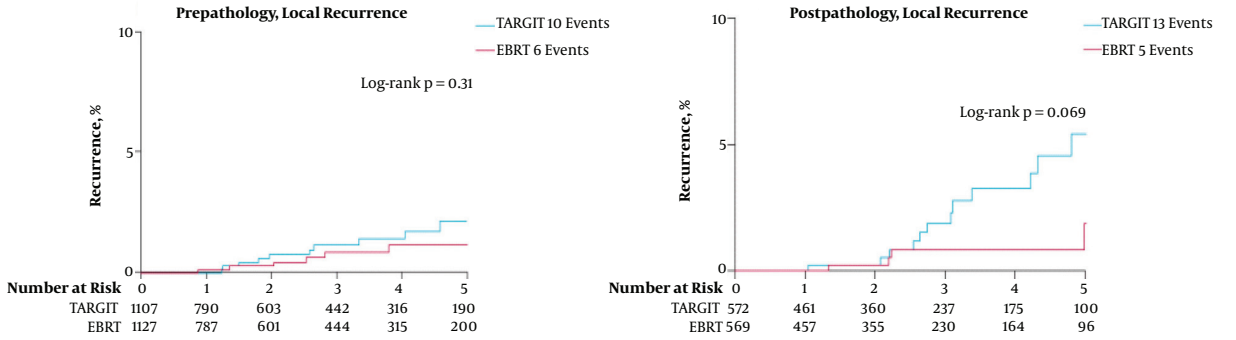

Figure 2. TARGIT-A study, local recurrence in pre-pathologic (Left), and post-pathologic (Right) conditions [with permission].

Table 5. Recurrence Rate in Trials Understudy

Recurrence	ELIOT 1305			TARGIT-A 3375		
	IORT 651[a]	EBRT 654[a]	Log Rank P Value	IORT[a]	EBRT[a]	P Value
In breast recurrence	35 (4.4)	4 (0.4)	-	-	-	-
Local	21 (2.5)	4 (0.4)	0.0003	23 (3.3)	11 (1.3)	0.042
Regional	61 (7.5)	21 (2.8)	-	46 (4.9)	37 (4.4)	-
Distant metastasis	33 (5.1)	35 (4.8)	0.94	(3.9)	(3.2)	
Group with risk factors 199 (30.6%) cases	11.3	-	-	-	-	-
Group without risk factors 452 (69.4%) cases	1.5	-	-	-	-	-

[a] Values are expressed as No. (%) or %.

Table 6. Breast and Non-Breast Mortality Rate in Trials Understudy

Death	ELIOT					TARGET-A				
	IORT	EBRT			P Value	IORT	EBRT			P Value
	Number	5-Year Event Rate	Number	5-Year Event Rate	-	Number	5-Year Event Rate	Number	5-Year Event Rate	-
Total death	34	1.7 - 4.7 (3.2%)	31	1.7 - 4.5 (3.1%)	0.59	37	1.5 - 4.3 (2.6%)	51	1.1 - 3.2 (1.9%)	-
Breast cancer	23	0.9 - 3.3 (2.1%)	20	0.9 - 3.2 (2%)	0.56	20	0.7 - 4.6 (1.8%)	16	-	0.56
Other cancers	11	0.2 - 2.0 (1.1%)	11	0.2 - 2.0 (1.1%)	0.93	17	0.8 - 2.5 (1.4%)	35	2.3 - 5.2 (3.5%)	0.0086

The database of ELIOT study on 1 822 cases from 2000 to 2008 were entered to GEC-ESTRO (Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology) classification. GEC-ESTRO recommended dividing patients with breast cancer to 3 groups according to the age, margin status, positive LN, and other characteristic to good, possible and contraindicated group for radical IORT.

According to this classification on ELIOT database, 537 patients (31.5%) included in good group with only 1 mm as negative margin, 468 patients (25.7%) in possible group, who were more than 40 years old and only 1 to 3 positive lymph nodes and close but clear margin < 1 mm and contraindicated group with 767 patients (42.2%), who had unfavorable characteristics like lymphovascular involvement, extensive intraductal (more than 25% DCIS) and more than 4 positive lymph nodes. Regarding these criteria, Table 8 shows the corresponding outcomes (14).

The local recurrence in the good group was only 1.9%, but this value in possible and contraindicated groups were more than 7%, and there was no difference in true recurrence and new ipsilateral cancer.

Table 7. Local Recurrence Rate After BCS Plus EBRT in Different Studies

Study	Local Recurrence, %
EORTC	4.3
START_B	2.8
Early breast cancer trialists' collaborative group (EBCTCG)	
LN+	11
LN-	6.7
TARGIT-A (IORT versus EBRT)	3.1 versus 1.3
MILAN III	2.3
Hungary PBRT	4.7
ELIOT (IORT versus EBRT)	4.4 versus 0.4

Table 8. LR, DM, and OS in ELIOT According to GEC-ESTRO Classification

Outcome	Good 573, 31.5% Event Rate, %		Possible 468, 25.7% Event Rate, %		Contraindicated 767, 42.2% Event Rate, %		Log Rank P Value
IBR	7	1.9	22	7.4	46	7.7	0.001
True recurrence	6	1.6	12	4.0	28	4.7	0.052
Ipsilateral new cancer	1	0.3	10	3.3	18	3.0	0.012
RNF	8	2.2	2	0.7	8	1.3	0.275
DM	5	1.4	5	1.7	23	3.9	0.016
DFS	34	90.8	42	85.9	110	81.5	0.004
CSS	3	99.2	4	98.7	24	96.0	0.014
OS	5	98.6	9	97.0	33	94.4	0.044

Abbreviations: IBR, in breast recurrence; RNF, regional node failure; DM, distant metastasis; DFS, disease-free survival; CSS, cause-specific survival; OS, overall survival.

With Regard to GEC-ESTRO recommendations, increased risk of recurrence is seen in age below 50 years, tumor size more than 2 cm, presence of LVI, multicentricity, and positive LN. Predictive factors for regional node failure (RNF) is T > 2 cm and for distant metastasis includes T > 2 cm, presence of lymphovascular invasion (LVI), and positive LN, which are not well-delineated in the ELIOT study.

According to ASTRO consensus guideline, which allocated the patients of ELIOT study in 3 groups of suitable, cautionary and unsuitable, 294 cases were classified as suitable, 691 as cautionary, and 812 as unsuitable, which means near half of them were not suitable for sole IORT treatment. The 5-years of ipsilateral breast recurrence rate in each group was 1.5% for suitable, 4.4% for cautionary, and 8.8% for unsuitable groups (15).

According to TARGIT-A study, all cases have undergone to 20 Gy dose in IORT, and patients with unfavorable characters (15%) also received EBRT after IORT. In patients, who received IORT concurrently with lumpectomy, only 1% increase recurrence rate (from 98% to 99% chance to being free of recurrence) was seen, but 2.3% decrease in non-breast cancer death in patients, who did not take EBRT after pathologic report, was obtained (9, 10).

Results of statistical analysis in comparing these two clinical trials showed that the favorable characters like old age, tumor sizes less than 2 cm, invasive ductal carcinoma, negative lymph nodes, or less positive nodes are more frequent in TARGIT-A with respect to the ELIOT one, and invasive lobular carcinoma and grade III are less in TARGIT-A study (significant P-value for all data). So, it seems that the considered criteria in TARGIT-A study for patient allocation in single dose IORT group are more similar to GEC-ESTRO and ASTRO.

Furthermore, 15% of IORT group, who had unfavorable characters, received EBRT; so, this may be the reason for reducing the rate of local recurrence in this study (16).

Comparison of ELIOT and TARGIT-A studies in their suitable groups, who undergone IORT concurrently with surgery, indicated that the local recurrence is 1.5% in the first and 2.1% in the second study.

4. Conclusions

IORT is a practice in partial breast radiation if the tumor characteristics, biomarkers, and demographic data are well considered. Two comprehensive clinical trials, including TARGIT-A and ELIOT were considered and their clinical outcomes were compared and evaluated. It can be concluded that the both trials are acceptable in the structures and related criteria, but due to the different characters and different analyses, the outcomes are different and non-comparable.

The outcome of using IORT is acceptable both with low energy X-ray or electron beam and suitable for breast cancer management without any damage to intra thoracic structures if eligibility criteria are more restricted.

Acknowledgments

None declared.

Footnotes

Authors' Contribution: None declared.

Conflict of Interests: The authors did not have any conflict of interests.

Financial Disclosure: No relevant financial or nonfinancial relationships to disclose.

References

1. Comas C, Prio A. [Intraabdominal preventive roentgen irradiation after surgery in a case of uterine cancer]. *Congres International d'Electrologie, Imprenta Francesca Badia*. Barcelona. 1991. French.
2. Krengli M, Calvo FA, Sedlmayer F, Sole CV, Fastner G, Alessandro M, et al. Clinical and technical characteristics of intraoperative radiotherapy. Analysis of the ISIORT-Europe database. *Strahlenther Onkol*. 2013;**189**(9):729–37. doi: 10.1007/s00066-013-0395-1. [PubMed: 23842635].
3. Gunderson LL, Willett CG, Calvo FA, Harrison LB. *Intraoperative irradiation: Techniques and results*. 2nd ed. Springer Science and Business Media: Humana press; 2011.
4. Abe M, Takahashi M. Intraoperative radiotherapy: The Japanese experience. *Int J Radiat Oncol Biol Phys*. 1981;**7**(7):863–8. doi: 10.1016/0360-3016(81)90001-8. [PubMed: 7198109].
5. Calvo F, Sole C, Herranz R, Lopez-Bote M, Pascau J, Santos A, et al. Intraoperative radiotherapy with electrons: Fundamentals, results, and innovation. *Ecancermedicalscience*. 2013;**7**:339. doi: 10.3332/ecancer.2013.339. [PubMed: 24009641]. [PubMed Central: PMC3757959].
6. Ratto C, Valentini V, Morganti AG, Barbaro B, Coco C, Sofo L, et al. Combined-modality therapy in locally advanced primary rectal cancer. *Dis Colon Rectum*. 2003;**46**(1):59–67. doi: 10.1097/01.DCR.0000038146.65224.90. [PubMed: 12544523].
7. Hashiguchi Y, Sekine T, Kato S, Sakamoto H, Nishimura Y, Kazumoto T, et al. Indicators for surgical resection and intraoperative radiation therapy for pelvic recurrence of colorectal cancer. *Dis Colon Rectum*. 2003;**46**(1):31–9. doi: 10.1097/01.DCR.0000039501.28199.CC. [PubMed: 12544519].
8. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. *Lancet Oncol*. 2013;**14**(13):1269–77. doi: 10.1016/S1470-2045(13)70497-2. [PubMed: 24225155].
9. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014;**383**(9917):603–13. doi: 10.1016/S0140-6736(13)61950-9. [PubMed: 24224997].
10. Vaidya JS, Baum M, Tobias JS, Massarut S, Wenz F, Murphy O, et al. Targeted intraoperative radiotherapy (TARGIT) yields very low recurrence rates when given as a boost. *Int J Radiat Oncol Biol Phys*. 2006;**66**(5):1335–8. doi: 10.1016/j.ijrobp.2006.07.1378. [PubMed: 17084562].
11. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. *Lancet*. 2010;**376**(9735):91–102. doi: 10.1016/S0140-6736(10)60837-9. [PubMed: 20570343].
12. Start Trialists' Group , Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, et al. The UK standardisation of breast radiotherapy (START) trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet Oncol*. 2008;**9**(4):331–41. doi: 10.1016/S1470-2045(08)70077-9. [PubMed: 18356109]. [PubMed Central: PMC2323709].
13. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;**366**(9503):2087–106. doi: 10.1016/S0140-6736(05)67887-7. [PubMed: 16360786].
14. Leonardi MC, Maisonneuve P, Mastropasqua MG, Morra A, Lazzari R, Dell'Acqua V, et al. Accelerated partial breast irradiation with intraoperative electrons: Using GEC-ESTRO recommendations as guidance for patient selection. *Radiother Oncol*. 2013;**106**(1):21–7. doi: 10.1016/j.radonc.2012.10.018. [PubMed: 23218711].
15. Leonardi MC, Maisonneuve P, Mastropasqua MG, Morra A, Lazzari R, Rotmensz N, et al. How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. *Int J Radiat Oncol Biol Phys*. 2012;**83**(3):806–13. doi: 10.1016/j.ijrobp.2011.08.014. [PubMed: 22245196].
16. Azria D, Lemanski C. Intraoperative radiotherapy for breast cancer. *Lancet*. 2014;**383**(9917):578–81. doi: 10.1016/S0140-6736(13)62304-1. [PubMed: 24224998].